

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of

SPRINGER et al.

Atty. Ref.: 620-358

Serial No. unknown

TC/A.U.: unknown

U.S. 371 of PCT/GB2003/003736

Filed: March 2, 2005

Examiner: Unknown

For: ENZYME ACTIVATED SELF-IMMOLATIVE N-SUBSTITUTED  
NITROGEN MUSTARD PRODRUGS

\* \* \* \* \*

March 2, 2005

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**INFORMATION DISCLOSURE STATEMENT**

As suggested by 37 C.F.R. 1.97, the undersigned attorney brings to the attention of the Patent and Trademark Office the references listed on the attached form PTO-1449. Copies of the International Search Report and references listed on form PTO-1449 are attached hereto.

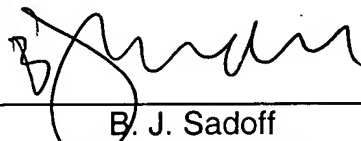
This is not to be construed as a representation that a search has been made or that no better prior art exists, or that a reference is relevant merely because cited.

The Examiner is requested to initial the attached form PTO-1449 and to return a copy of the initialed document to the undersigned as an indication that the attached references have been considered and made of record.

Respectfully submitted,

**NIXON & VANDERHYTE P.C.**

By: \_\_\_\_\_

  
B. J. Sadoff  
Reg. No. 36,663

BJS:alb  
1100 North Glebe Road, 8th Floor  
Arlington, VA 22201-4714  
Telephone: (703) 816-4000  
Facsimile: (703) 816-4100

INFORMATION DISCLOSURE  
CITATION

ATTY. DOCKET NO.

620-358

AL NO.

10/526173

unknown - U.S. 371 of  
PCT/GB2003/003736

APPLICANT

SPRINGER et al.

(Use several sheets if necessary)

FILING DATE

March 2, 2005

TC/A.U.

unknown

## U.S. PATENT DOCUMENTS

*EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO
90/02729	22 March 1990	WO	C07C	237/30	
91/03460	21 March 1991	WO	C07C	237/36	
94/25429	10 November 1994	WO	C07C	237/36	
95/02420	26 January 1995	WO			
95/03830	09 February 1995	WO	A61K	47/48	
96/22277	25 July 1996	WO	C07C	275/32	
96/03151	08 February 1996	WO	A61K	48/00	
96/03515	08 February 1996	WO	C12N	15/57	
97/26918	31 July 1997	WO	A61K	47/48	
00/58271	05 October 2000	WO	C07C	237/36	
02/060862	08 August 2002	WO	C07C	269/04	

## OTHER DOCUMENTS (including Author, Title, Date, Pertinent pages, etc.)

	Bagshawe et al., 1988, "A Cytotoxic Agent Can Be Generated Selectively At Cancer Sites," <u>British Journal of Cancer</u> , Vol. 58, pp. 700-703.
	Bagshawe et al., 1994, "Antibody-Directed Enzyme Prodrug Therapy (ADPET): A Review of Some Theoretical, Experimental and Clinical Aspects," <u>Analytical Oncology</u> , Vol. 5, pp. 879-891.
	Denny and Wilson, 1998, "The Design of Selectively-Activated Anti-Cancer Prodrugs for Use in Antibody-Directed and Gene-Directed Enzyme Prodrug Therapies," <u>Journal of Pharmaceutical Pharmacology</u> , Vol. 50, pp. 387-394.
	Deonarain and Epenetos, 1994, "Targeting Enzymes for Cancer Therapy: Old Enzymes in New Roles," <u>British Journal of Cancer</u> , Vol. 70, pp. 786-794.
	Dowell et al., 1996, "New Mustard Prodrugs for Antibody-Directed Enzyme Prodrug Therapy: Alternative for the Amide Link," <u>Journal of Medicinal Chemistry</u> , Vol. 39, pp. 1100-1105.
	Encell and Loeb, 1998, "Improving Enzymes for Cancer Gene Therapy," <u>Tumor Targeting</u> , Vol. 3, p. 191.
	Ferez, C. R., et al., 1989, <u>Journal of Labelled Compounds &amp; Radiopharmaceuticals</u> , Vol. 27, pp. 737-751.
	Friedlos, F.; Davies, L.; Scanlon, I.; Ogilvie, L. M.; Martin, J.; Stribbling, S. M.; Niculescu-Duvaz, I.; Marais, R.; Springer, C. J., 2002, "Three new prodrugs for suicide gene therapy using CPG2 all elicit improved bystander effect efficacy in two xenograft models," <u>Cancer Research</u> , Vol. 62, pp. 1724-1729.
	Hay and Denny, 1996, "Antibody-Directed Enzyme Prodrug Therapy (ADEPT)," <u>Drugs of the Future</u> , Vol. 21, pp. 917-931.
	Jungheim and Shepherd, 1994, "Design of Antitumour Prodrugs: Substrates for Antibody Targeted Enzymes," <u>Chemical Reviews</u> , Vol. 94, pp. 1553-1566.
	Kirn, D., 2000, "Replication-selective microbiological agents fighting cancer with targeted germ ware," <u>Journal of Clinical Investigation (JCI)</u> , Vol. 105, No. 7, pp. 837-839.

\*Examiner

Date Considered

Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

INFORMATION DISCLOSURE  
CITATION

ATTY. DOCKET NO.

620-358

AL NO.

10/526173  
unknown - U.S. 371 of  
PCT/GB2003/003736

APPLICANT

SPRINGER et al.

(Use several sheets if necessary)

FILING DATE

March 2, 2005

TC/A.U.

unknown

	Marais, R.; Spooner, R. A.; Stribbling, S. M.; Light, Y.; Martin, J.; Springer, C. J. S., 1997, "A cell surface tethered enzyme improves efficiency in gene-directed enzyme prodrug therapy," <u>Nature Biotechnology</u> , Vol. 15, pp. 1373-1377.
	Martin, J.; Stribbling, S. M.; Poon, G. K.; Begent, R. H. J.; Napier, M.; Sharma, S. K.; Springer, C. J., 1997, "Antibody-directed enzyme prodrug therapy: Pharmacokinetics and plasma levels of prodrug and drug in a phase I clinical trial," <u>Cancer Chemotherapy and Pharmacology</u> , Vol. 40, pp. 189-201.
	Matthews, 1988, "Structural Basis of the Action of Thermolysin and Related Zinc Peptidases," <u>Accounts of Chemical Research</u> , Vol. 21, pp. 333-340.
	Melton and Sherwood, 1996, "Antibody-Enzyme Conjugates for Cancer Therapy," <u>Journal of the National Cancer Institute</u> , Vol. 88, pp. 153-165.
	Minton et al., 1984, "The Complete Nucleotide Sequence of the Pseudomonas Gene Coding for Carboxypeptidase G2," <u>Gene</u> , Vol. 31, pp. 31-38.
	Napier, M. P.; Sharma, S. K.; Springer, C. J.; Bagshawe, K. D.; Green, A. J.; Martin, J.; Stribbling, S. M.; Cushen, N.; O'Malley, D.; Begent, R. H. J., 2000, "Antibody-directed enzyme prodrug therapy: Efficacy and mechanism of action in colorectal carcinoma," <u>Clinical Cancer Research</u> , Vol. 6, pp. 765-772.
	Niculescu-Duvaz and Springer, 1995, "Antibody-Directed Enzyme Prodrug Therapy (ADEPT): A Targeting Strategy in Chemotherapy," <u>Current Medicinal Chemistry</u> , Vol. 2, pp. 687-706.
	Niculescu-Duvaz and Springer, 1996, "Development of Prodrugs for ADEPT (Antibody-Directed Prodrug Therapy)," <u>Expert Opinion on Investigational Drugs</u> , Vol. 3, pp. 289-308.
	Niculescu-Duvaz and Springer, 1997, "Gene-Directed Enzyme Prodrug Therapy: A Review of Enzyme/Prodrug Combinations," <u>Expert Opinion on Investigational Drugs</u> , Vol. 6, pp. 685-703.
	Niculescu-Duvaz et al., 1998a, "Gene-Directed Enzyme Prodrug Therapy," <u>Bioconjugate Chemistry</u> , Vol. 9, pp. 4-22.
	Niculescu-Duvaz et al., 1999, "Prodrugs for antibody- and gene-directed enzyme prodrug therapies (ADEPT and GDEPT)," <u>Anti-Cancer Drug Design</u> , Vol. 14, pp. 517-538.
	Niculescu-Duvaz et al., 1999, "Self-Immolative Anthracycline Prodrugs for Suicide Gene Therapy," <u>J. Med. Chem.</u> , Vol. 42, pp. 2485-2489.
	Niculescu-Duvaz et al., 1999a, "Recent Developments in Gene-Directed Enzyme Prodrug Therapy (GDEPT) for cancer," <u>Current Opinion in Molecular Therapeutics</u> , Vol. 1, pp. 480-486.
	Niculescu-Duvaz et al., 2003, "Self-Immolative Nitrogen Mustard Prodrug Cleavable by Carboxypeptidase G2 (CPG2) Showing Large Cytotoxicity Differentials in GDEPT," <u>J. Med. Chem.</u> , Vol. 46, No. 9, pp. 1690-1705.
	Niculescu-Duvaz, D.; Niculescu-Duvaz, I.; Friedlos, F. F.; Martin, J.; Spooner, R.; Davies, L.; Marais, R.; Springer, C. J., 1998b, "Self-immolative mustard prodrugs for suicide gene therapy," <u>Journal of Medicinal Chemistry</u> , Vol. 41, pp. 5297-5309.
	Rowell et al., 1997, "Crystal Structure of Carboxypeptidase G2, a Bacterial Enzyme with Applications in Cancer Therapy," <u>Structure</u> , Vol. 5, pp. 337-347.
	Roth and Cristiano, 1997, "Gene Therapy for Cancer: What Have We Done And Where Are We Going?," <u>Journal of the National Cancer Institute</u> , Vol. 89, pp. 21-39.
	Satchi and Duncan, 1998, "PDEPT: polymer-directed enzyme prodrug therapy," <u>British Journal of Cancer</u> , Vol. 78, No. 2, pp. 149-150.
	Senter et al., 1993, "Generation of Cytotoxic Agents by Targeted Enzymes," <u>Bioconjugate Chemistry</u> , Vol. 4., pp. 3-9.
	Sherwood et al., 1985, "Purification and Properties of Carboxypeptidase G2 Pseudomonas sp strain RS-16," <u>European Journal of Biochemistry</u> , Vol. 148, pp. 447-453.

\*Examiner

Date Considered

Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

INFORMATION DISCLOSURE  
CITATION

ATTY. DOCKET NO.

620-358

AL NO.

10/526173  
unknown - U.S. 371 of  
PCT/GB2003/003736

APPLICANT

SPRINGER et al.

(Use several sheets if necessary)

FILING DATE

March 2, 2005

TC/A.U.

unknown

	Spooner, R.; Martin, J.; Friedlos, F.; Marais, R.; Springer, C. J., 2000, "In suicide gene therapy, the site of subcellular localization of the activating enzyme is more important than the rate at which it activates prodrug," <u>Cancer Gene Therapy</u> , Vol. 7, pp. 1348-1356.
	Springer and Niculescu-Duvaz, 1995, "Antibody-Directed Enzyme Prodrug Therapy (ADEPT) with mustard prodrugs," <u>Anti-Cancer Drug Design</u> , Vol. 10, pp. 361-362.
	Springer and Niculescu-Duvaz, 1999, "Patent Property of Prodrugs Involving Suicide Gene Therapy," <u>Expert Opinion on Therapeutic Patents</u> , Vol. 9, pp. 1381-1388.
	Springer and Niculescu-Duvaz, 2000, "Prodrug-activating systems in suicide gene therapy", <u>The Journal of Clinical Investigation</u> , Vol. 105, pp. 1161-1167.
	Springer et al., 1990a, "Novel Prodrugs Which Are Activated to Cytotoxic Alkylating Agents by Carboxypeptidase G2," <u>Journal of Medicinal Chemistry</u> , Vol. 33, pp. 677-681.
	Springer et al., 1994, "Novel Prodrugs of Alkylating Agents Derived from 2-Fluoro- and 3-Fluorobenzoic Acids for Antibody-Directed Enzyme Prodrug Therapy", <u>Journal of Medicinal Chemistry</u> , Vol. 37, pp. 2361-2370.
	Springer et al., 1995a, "The Design of Prodrugs for Antibody Directed Enzyme Prodrug Therapy (ADEPT)," in <u>New Antibody Technologies and the Emergence of Useful Cancer Therapy</u> , Begent, R., Hamlin, A., editors (The Royal Society of Medicine Press: London), pp. 75-77.
	Springer et al., 1995b, "Optimization of Alkylating Prodrugs Derived from Phenol and Aniline Mustards: A New Clinical Candidate Prodrug (ZD2767) for ADEPT," <u>Journal of Medicinal Chemistry</u> , Vol. 38, pp. 5051-5065.
	Wakselman, 1983, "1,4 and 1,6 Eliminations from Hydroxy- and Amino-Substituted Benzyl Systems: Chemical and Biochemical Applications," <u>Nouveau Journal de Chemie</u> , Vol. 7, pp. 439-447.
	Zhang et al., 1995, "Advances in Cancer Gene Therapy," <u>Advances in Pharmacology</u> , Vol. 12, pp. 289-341.
	International Search Report of PCT/GB03/03736

\*Examiner

Date Considered

Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.